

What is claimed is:

1. A method for preparing trans-capsaicin, comprising:
 - a) alkylating 3-methyl butyne with halovaleric acid or to obtain 8-methyl-6-nonynoic acid;
 - b) reducing said 8-methyl-6-nonynoic acid to obtain trans-8-methyl-6-nonenoic acid;
 - c) activating said 8-methyl-6-nonenoic acid to obtain an acid halide or activated acid derivatives; and
 - d) acylating 4-hydroxy-3-methoxybenzylamine hydrochloride with said acid halide to obtain trans-capsaicin.
2. The method of claim 1, wherein step a) comprises alkylating 3-methyl butyne with ω -haloalkanic acid to obtain ω -alkynolic acid analogues.
3. The method of claim 1, wherein step a) comprises the steps of:
 - i) mixing anhydrous tetrahydrofuran with hexamethylphosphoramide and cooling said mixture to about -78°C to about -60°C;
 - ii) adding to said mixture of step i) 3-methyl butyne followed by a dropwise addition of a base at a temperature from about -78°C to about -65°C to obtain a second mixture;
 - iii) warming said second mixture up to about -30°C while stirring; and
 - iv) adding dropwise a halovaleric acid in anhydrous tetrahydrofuran at a temperature of about -30°C, said halovaleric acid added in a sufficient amount to convert said 3-methyl butyne to said 8-methyl-6-nonynoic acid, then gradually warming to room temperature and stirring to obtain a reaction mixture.
4. The method of claim 2, further comprising:
 - i) adding hydrochloric acid to said reaction mixture and extracting said reaction mixture with ethyl acetate; and
 - ii) washing said extracted reaction mixture with brine to yield a crude product.
5. The method of claim 3, further comprising:
 - i) purifying said crude product; and
 - ii) removing solvents under vacuum to provide a step a) intermediate product.

6. The method of claim 5, wherein said crude product is purified by column chromatography.
7. The method of claim 5, wherein said crude product is purified by acid-base extraction.
8. The method of claim 5, wherein said crude product is purified by vacuum distillation.
9. The method of claim 5, wherein said step a) intermediate product is 8-methyl-6-nonynoic acid.
10. The method of claim 3, wherein said halovaleric acid is selected from the group consisting of bromovaleric acid, chlorovaleric acid, fluorovaleric acid, iodovaleric acid and astatinovaleric acid, 1-mesyloxyvaleric acid, 1-tosyloxyvaleric acid.
11. The method of claim 10, wherein said halovaleric acid is bromovaleric acid.
12. The method of claim 3, wherein 1,2-dimethyl-3,4,5,6-tetrahydro-(1H) pyrimidinone is substituted for hexamethylphosphoramidate in step i).
13. The method of claim 4, wherein said base is selected from the group consisting of *n*-BuLi, *sec*-BuLi, *t*-BuLi, lithium di(isopropyl) amide, sodium hydride, sodium amide, lithium amide, methyl lithium, methyl magnesium bromide, ethyl magnesium bromide, alkyl or aryl magnesium halides or mixture thereof.
14. The method of claim 13, wherein said base is *n*-butyllithium.
15. The method of claim 1, wherein step b) comprises the steps of:
 - i) dissolving said 8-methyl-6-nonynoic acid in a mixture of anhydrous tetrahydrofuran and *t*-butyl alcohol to obtain a solution and cooling said solution to about -55°C to about -40°C ;
 - ii) condensing ammonia to said solution to a temperature of about -50°C to about -33°C;
 - iii) adding sodium piece-wise and stirring at a temperature from about -45°C to about -30°C and stirring for a sufficient period of time to dissolve said sodium, and

iv) adding ammonium chloride, warming to room temperature and allowing the ammonia to evaporate to obtain a reaction mixture.

16. The method of claim 15, wherein additional lithium is added after step iii).
17. The method of claim 15, wherein step iii) comprises adding lithium at a temperature from about -65°C to about -45°C and stirring for a sufficient period of time to dissolve said lithium.
18. The method of claim 15, further comprising:
 - i) adding water to said reaction mixture;
 - ii) acidifying said reaction mixture with hydrochloric acid to a pH of about 2 to about 3;
 - iii) extracting said reaction mixture with ethyl acetate, washing with brine and drying over anhydrous sodium sulfate; and
 - iv) filtering and removing solvents under vacuum to obtain a step b) intermediate product.
19. The method of claim 18, wherein said step b) intermediate product is trans-8-methyl-nonenoic acid.
20. The method of claim 17, wherein step ii) is omitted.
21. The method of claim 15, wherein lower alkyl amines are substituted for said ammonium of step ii).
22. The method of claim 15, wherein sodium is substituted for said lithium of step iii).
23. The method of claim 15, wherein secondary butyl alcohol (*sec*-BuOH), ethyl alcohol (EtOH), or other alkyl alcohols are substituted for said *t*-butyl alcohol of step i).
24. The method of claim 15, wherein lithium and liquid ammonia or sodium and liquid ammonia are substituted for said lithium, said tetrahydrofuran and said liquid ammonia.
25. The method of claim 17, further comprising the steps of:
 - i) stirring said reaction mixture overnight to evaporate said ammonia ;

- ii) adding additional anhydrous tetrahydrofuran and ammonium chloride, stirring said mixture for a sufficient time to neutralize excess lithium;
 - iii) adding ice-water portionwise;
 - iv) extracting said mixture with ethyl acetate, washing with brine and drying over anhydrous sodium sulfate; and
 - v) filtering and removing solvents under vacuum to produce a step b) intermediate product.
26. The method of claim 17, further comprising the steps of:
- i) cooling the reaction mixture and quenching with ice-water;
 - ii) acidifying said mixture with hydrochloric acid added portion-wise to a pH of about 2 to about 3;
 - iii) extracting said mixture with ethyl acetate, washing with brine and drying over anhydrous sodium sulfate;
 - iv) filtering and concentrating under vacuum at a temperature of about 30°C to obtain a crude product.
27. The method of claim 26, further comprising the step of purifying said product by flash column chromatography to obtain a step b) intermediate product.
28. The method of claim 26, further comprising the step of purifying said crude product by vacuum distillation.
29. The method of claim 1, wherein step c) comprises the steps of:
- i) adding dropwise a thionyl halide to said 8-methyl-6-nonenoic acid at room temperature to form a solution;
 - ii) heating said solution at about 50°C to about 75°C for a sufficient period of time to convert said 8-methyl-6-nonenoic acid to said acid halide; and
 - iii) removing excess thionyl halide under vacuum to obtain a step c) intermediate product.
30. The method of claim 29, wherein said thionyl halide is thionyl bromide.
31. The method of claim 29, wherein said thionyl halide is thionyl chloride.

32. The method of claim 29, wherein said step c) intermediate product is an acid halide.
33. The method of claim 32, wherein said acid halide is acid bromide.
34. The method of claim 32, wherein said acid halide is acid chloride.
35. The method of claim 32, wherein said acid halide is an activated carboxylic acid.
36. The method of claim 35, wherein said activated carboxylic acid is an imidazolid.
37. The method of claim 35, wherein said activated carboxylic acid is an carbodiimide.
38. The method of claim 1, wherein step d) comprises the steps of:
 - i) mixing 4-hydroxy-3-methoxy benzylamine hydrochloride and dimethylformamide;
 - ii) adding portion-wise at room temperature to said mixture of step i) aqueous sodium hydroxide and stirring to obtain a reaction mixture;
 - iii) adding acid halide in anhydrous ether at a temperature of about 0°C to about 10°C for a sufficient period of time to convert said acid halide to an amide; and thereafter
 - iv) gradually warming said mixture to room temperature and stirring.
39. The method of claim 38, further comprising the steps of:
 - i) adding water to said mixture and extracting said mixture with ethyl acetate to obtain an ethyl acetate extract;
 - ii) washing said extract with hydrochloric acid and, thereafter, washing with sodium bicarbonate;
 - iii) washing said solution with brine and drying over anhydrous sodium sulfate;
 - iv) filtering and removing solvents under vacuum to obtain a crude trans capsaicin product.
40. The method of claim 39, further comprising the steps of:
 - i) purifying said crude product by column chromatography to obtain trans-capsaicin product.

41. The method of claim 38, wherein potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, or an alkyl amine is substituted for said aqueous sodium hydroxide of step ii).
42. The method of claim 38, wherein 4-hydroxy-3-methoxy benzylamine is substituted for said 4-hydroxy-3-methoxy benzylamine hydrochloride of step i).
43. The method of claim 41, wherein said alkyl amine is selected from the group consisting of triethylamine, Hunig's base, 4-dimethylaminopyridine and pyridine.
44. The method of claim 38, wherein tetrahydrofuran, 2-dimethoxyethane, acetonitrile, dichloromethane, chloroform, or methyl ethyl ketone is substituted for said dimethylformamide in step i).
45. A method of purifying the trans-capsaicin product of claim 35, comprising the steps of:
 - i) dissolving said crude trans-capsaicin product in a mixture of ether/hexane and heating said mixture to about 40°C to about 45°C;
 - ii) cooling said mixture to room temperature or below room temperature; and
 - iii) filtering said mixture to provide a purified trans-capsaicin product.
46. The method of claim 45, wherein step iii) comprises filtering said mixture and washing said mixture with a mixture of ether/hexane and drying under vacuum to obtain a purified trans-capsaicin product.
47. The method of claim 1, further comprising purifying said trans-capsaicin using a semi-preparative HPLC.
48. The method of claim 39, further comprising purifying said crude trans-capsaicin product using a semi-preparative HPLC.
49. The method of claim 40, further comprising purifying said trans-capsaicin product using a semi-preparative HPLC.

50. The method of claim 47, wherein the purification using the semi-preparative HPLC provides for a resulting ultra-purified trans-capsaicin having a purity of about 97% or greater capsaicin.
51. The method of claim 47, wherein the purification using the semi-preparative HPLC provides for a resulting ultra-purified trans-capsaicin having a purity of about 98% or greater capsaicin.
52. The method of claim 47, wherein the purification using the semi-preparative HPLC provides for a resulting ultra-purified trans-capsaicin having a purity of about 99% or greater capsaicin.
53. The trans-capsaicin product produced by the method of claim 47.
54. A capsaicin composition for relieving pain at a site in a human or animal in need thereof consisting essentially of pure trans capsaicin.
55. The composition of claim 54, wherein said trans capsaicin is used for the treatment of nociceptive pain, neuropathic pain, pain from nerve injury, pain from neuralgia, pain from myalgias, pain associated with painful trigger points, pain from tumors in soft tissues, pain associated with neurotransmitter-dysregulation syndromes and pain associated with orthopedic disorders.
56. The composition of claim 54, wherein said trans capsaicin is used for the treatment of orthopedic disorders selected from the group consisting of conditions of the foot, knee, hip, spine, shoulders, elbow, hand, head and neck.
57. The composition of claim 54, wherein said pure trans capsaicin is provided in an injectable formulation.
58. A trans-capsaicin compound comprising about 97% or greater trans-capsaicin.
59. A trans-capsaicin compound comprising about 98% or greater trans-capsaicin.

60. A trans-capsaicin compound comprising about 99% or greater trans-capsaicin.
61. A pharmaceutical composition comprising an ultra-purified trans-capsaicin compound comprising about 97% or greater trans-capsaicin, about 98% or greater trans-capsaicin, or about 99% or greater trans-capsaicin and a vehicle suitable for infiltration or injection.
62. The pharmaceutical composition of claim 61, wherein said vehicle comprises about 20% PEG 300, about 10 mM histidine and about 5% sucrose in water for injection.